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Editorials

Tuberculosis in the European Union – ongoing commitment needed to control the disease

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On 24 March 1882, the German microbiologist Robert Koch announced his discovery that the bacterium *Mycobacterium tuberculosis* caused tuberculosis (TB). He was awarded a Nobel prize for these findings in 1905. World TB day on 24 March commemorates this event and is an opportunity for a critical appraisal of the TB situation, for raising awareness and for joining forces in order to control the disease. It is estimated that every year, there are over nine million new cases of TB worldwide and around one and a half million people die from TB. Thus TB is still one of the most important infectious diseases causing death in humans.

In the European Union (EU), considerable progress has been made in preventing and controlling the disease: The number of newly diagnosed cases and the overall notification rate declined continuously in the past decade. The notification rate in 2007 was 12% lower than in 2003, which reflects a downward trend in 25 countries [1]. In spite of this decline, a total of 84,917 new cases of TB were registered in 2007 – half a century after the introduction of effective treatment – in the EU and the three countries in the European Economic Area/European Free Trade Association (EEA/EFTA) Iceland, Liechtenstein and Norway.

In March 2009, the European Centre for Disease Prevention and Control (ECDC) and the World Health Organization Regional Office for Europe (WHO/Europe) publish their first joint report on the *Surveillance of tuberculosis in Europe – 2007* since the coordination of the former EuroTB network moved to ECDC on 1 January 2008 and the two organisations started to perform joint surveillance.

While the figures from this report for the EU and EEA/EFTA countries are encouraging, they also highlight a number of challenges that hamper the progress towards the elimination of TB.

Multidrug-resistant (MDR) TB, a form of TB which is difficult to cure and laborious for the patient, and which requires considerable human and financial resources, threatens the goal of eliminating TB in Europe. High proportions of MDR TB – up to 21% of all TB cases – are observed in some EU countries. In this issue of *Eurosurveillance* an article by Anderson et al. shows trends in MDR TB in Scotland, a low incidence country for TB, over eight years and aims at identifying risk groups that need special attention [1]. A rapid communication based on the 2007 TB Surveillance report, shows a disparity in TB incidence within the EU [2], where the majority of countries are progressing towards elimination of the disease (defined as less than one case per 1,000,000 population per year) and where TB tends to accumulate in vulnerable populations with poor access to healthcare. An article by Mulder *et al*. illustrates relevant aspects of TB in individuals migrating form high incidence countries [3], and an article from Greece points out considerable underreporting for a particular region in this EU Member State [4].

The ECDC/WHO/Europe surveillance report also shows that some countries in the EU are still confronted with considerable numbers of newly diagnosed TB cases and notification rates from 36 to 118 cases per 100,000 population. These countries need particular support, and ECDC is closely collaborating with them to jointly face the challenges.

TB has been high on ECDC's agenda from start; the ECDC TB programme comprises a multi-disciplinary team of experts working together on all aspects of the disease to support the countries in their progress towards elimination of TB, a goal that requires sustained political commitment and equal access to early diagnosis, treatment and cure for all patients.

On request of the European Commission, ECDC will be supporting the follow-up of the *Framework Action Plan to Fight Tuberculosis in the EU* [5] in the coming months and will work closely with Member States and experts in the field to define the most effective manner of its implementation. We are certain that this will contribute to sustain the efforts towards TB elimination despite the obstacles that lie ahead.

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Tuberculosis in the EU and EEA/EFTA countries - what is the latest data telling us?

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Since 1 January 2008, the European Centre for Disease Prevention and Control (ECDC) and the World Health Organization Regional Office for Europe (WHO/Europe) jointly coordinate the tuberculosis (TB) surveillance activities in Europe. The data collected provides an opportunity for a comprehensive analysis of the TB situation. We aimed at analysing the EU and EEA/EFTA data to identify general TB trends and to provoke some discussion regarding the challenges and needs for monitoring the epidemic.

Background

Since 1 January 2008, the European Centre for Disease Prevention and Control (ECDC) and the World Health Organization Regional Office for Europe (WHO/Europe) coordinate jointly the tuberculosis (TB) surveillance activities in Europe. The aim of this coordinated surveillance is to ensure a high quality of TB standardized data covering all 53 countries in the WHO European Region* and Liechtenstein. Designated national surveillance institutions are responsible for reporting the data. The surveillance data are submitted to and are validated in separate systems maintained by each organisation, which then feed into a joint database for the analysis.

The data provided by the 27 European Union (EU) Member States and three European Economic Area and European Free Trade Association (EEA/EFTA) countries (Iceland, Norway and Liechtenstein) provide an opportunity for assessing the TB epidemiological situation in more detail. In this paper we analyse in more detail the case-based data submitted to The European Surveillance System (TESSy) managed by the ECDC, including cases notified during 2007 and the updated data for treatment outcome monitoring for cases starting treatment in 2006.

The objective of this analysis is to identify general TB trends and to provoke some discussion regarding the challenges and needs for monitoring the epidemic that, despite a high level of heterogeneity among EU Member States, has shown a steadily declining trend over the past 10 years. To help understand better whether this decline is supported by other epidemiological indicators, a summary analysis of the case reporting, treatment outcomes and TB mortality, as well as trends in reported TB drug resistance, are presented.

TB case reporting and trends

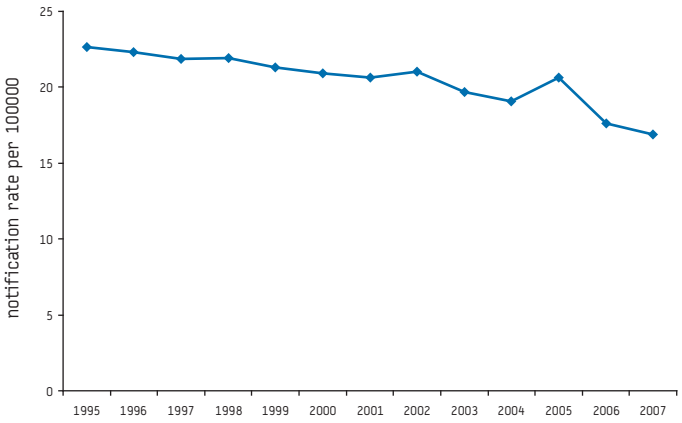
The 27 countries of the EU, plus Iceland, Norway and Liechtenstein reported 84,917 TB cases in 2007, representing 18% of the total number of cases in the WHO European Region (53 countries and Lichtenstein). TB notification rates were highest in Romania (118 per 100,000) and Bulgaria (40) – both cointries joined the EU in 2007 – and in the Baltic States (range 36-71). The overall rate for the EU and EEA/EFTA countries was 17 per 100,000.

Between 2003 and 2007, the overall notification rates decreased by a mean of 3.8% annually (Figure 1). However, substantial increases were observed in Malta (+61% mean per year) and Iceland (+37% mean per year) while some increases were also reported in Ireland and Greece (+2%), United Kingdom (+3% mean per year) and Sweden (+5% mean per year), although in the latter two countries this trend has reversed in recent years.

Paediatric TB cases represented 4% of notified cases of both national and foreign origin. This proportion of TB cases in children has been stable for the last 10 years. In contrast, the middle-aged (45-64 years) and the elderly (>64 years) together represented

Figure 1

Trend of TB notification rate for the 27 EU and Iceland and Norway, 1995-2007



Source: EuroTB (up to 2006) and ECDC (from 2006). Population figures from EUROSTAT.
Note: LIECHTENSTEIN data not available for the whole period and therefore not included

more than half of the cases of national origin (natives) but only 28% of the cases of foreign origin.

Overall the trend of the proportion of TB cases attributable to foreign origin has remained stable over the period 2005, 2006 and 2007. However in the same period, a decrease of over 4% was recorded in Germany, Italy and Lithuania. In 2007, 21% of cases (range: 0-78% for all countries) were of foreign origin, two-thirds of whom originated from Asia or Africa and 6% from the former Soviet Union (FSU). Most cases of foreign origin were reported among younger adults, especially in the 25-44 year age group (53%).

Over the period 2003 to 2007, the rate of TB meningitis in children under 5 years remained below 1.0 per 10 million general population in most EU and EEA/EFTA countries. Rates above 1.0 for two consecutive years or more were reported by Austria (TB case rate of 10.5/100,000 in 2007 for all forms of TB), as well as Lithuania, and Romania (total TB rates >30).

Treatment outcomes and mortality trends

In 21 countries with outcome data considered to be complete (for 2006), treatment success was reported in 80% of new definite pulmonary cases, representing a 7% increase from 2001 (Figure 2). The proportion of cases lost to follow up has decreased since 2001 but was more frequent among foreign-born cases than nationals (35% vs 16% respectively in 2006, all pulmonary cases) while death was less frequently reported (4% vs 8%).

In all EU countries, TB mortality rates have decreased or remained stable over recent years. A net decrease exceeding 10% per year over four consecutive years was observed in the Czech Republic, Finland, Greece, and Hungary.

Table 1

Tuberculosis cases, case rates per 100,000 population and mean annual change in rates, EU and EFTA/EEA countries, 2003-2007

Country	2003		2004		2005		2006		2007		Mean annual % change in rate, 2003-2007
	N	Rate	N	Rate	N	Rate	N	Rate	N	Rate	
Austria	980	12.1	1,061	13.0	999	12.1	873	10.5	874	10.5	-3.1%
Belgium	1,117	10.8	1,198	11.5	1,107	10.6	1,127	10.7	1,028	9.7	-2.4%
Bulgaria	3,263	41.7	3,232	41.5	3,302	42.7	3,232	42.0	3,052	39.8	-1.1%
Cyprus	35	4.8	30	4.1	37	4.9	37	4.8	42	5.3	3.4%
Czech Republic	1,162	11.4	1,057	10.3	1,007	9.8	973	9.5	871	8.4	-7.2%
Denmark*	393	7.3	385	7.1	422	7.8	377	6.9	391	7.2	-0.2%
Estonia	623	46.0	594	44.0	519	38.6	455	33.9	487	36.3	-5.4%
Finland	412	7.9	331	6.3	361	6.9	299	5.7	313	5.9	-6.1%
France	6,098	9.8	5,514	8.8	5,374	8.6	5,336	8.4	5,588	8.8	-2.6%
Germany	7,166	8.7	6,542	7.9	6,020	7.3	5,402	6.6	5,020	6.1	-8.4%
Greece	620	5.6	774	7.0	769	6.9	681	6.1	659	5.9	2.0%
Hungary	2,582	25.5	2,340	23.2	1,964	19.5	1,894	18.8	1,752	17.4	-9.0%
Iceland	5	1.7	12	4.1	11	3.7	13	4.3	14	4.5	37.2%
Ireland	407	10.2	432	10.6	450	10.8	458	10.7	478	10.9	1.8%
Italy	4,518	7.8	4,220	7.3	4,137	7.1	4,387	7.4	4,527	7.6	-0.6%
Latvia	1,726	74.2	1,610	69.6	1,443	62.7	1,328	58.0	1,255	55.1	-7.1%
Liechtenstein	0	-	0	-	0	-	0	-	5	14.2	-
Lithuania	2,821	81.7	2,514	73.2	2,574	75.4	2,559	75.4	2,408	71.3	-3.2%
Luxembourg	54	12.0	31	6.8	37	8.0	33	7.0	39	8.1	-5.3%
Malta	7	1.8	19	4.7	25	6.2	30	7.4	38	9.3	61.4%
Netherlands	1,321	8.1	1,344	8.3	1,155	7.1	1,021	6.2	960	5.9	-7.7%
Norway	337	7.4	302	6.6	288	6.2	294	6.3	307	6.5	-2.9%
Poland	10,124	26.5	9,493	24.9	9,280	24.3	8,593	22.5	8,616	22.6	-3.9%
Portugal	4,148	39.7	3,854	36.7	3,573	33.9	3,423	32.3	3,127	29.5	-7.2%
Romania	31,039	142.8	31,034	143.1	29,289	135.4	27,319	126.5	25,491	118.3	-4.5%
Slovakia	983	18.3	705	13.1	760	14.1	730	13.5	682	12.6	-7.8%
Slovenia	293	14.7	263	13.2	278	13.9	215	10.7	218	10.8	-6.7%
Spain	7,467	17.8	7,766	18.2	7,820	18.0	8,029	18.2	7,767	17.3	-0.6%
Sweden	408	4.6	461	5.1	559	6.2	497	5.5	491	5.4	4.9%
United Kingdom	7,220	12.1	7,609	12.7	8,317	13.8	8,498	14.0	8,417	13.8	3.4%
Total	**97 329**	**19.8**	**94 727**	**19.1**	**91 877**	**18.5**	**88,113**	**17.7**	**84,917**	**16.9**	**-3.8%**

Drug resistance

Twenty nine countries, (all except Poland) reported resistance data for cases notified in 2007. Data from 22 countries that performed culture and Drug Sensitivity Testing (DST) routinely in 2007, or provided DST results as part of a national case-linked dataset, were considered to be representative. Multi-drug resistance (MDR) remained more frequent in the Baltic States, with the proportion of combined MDR cases (all MDR cases regardless of previous treatment history) ranging from 10 to 21%, than in the other countries (range: 0-4%). Rates have remained relatively stable over the past years in the Baltic countries and it remains to be seen if the recent decreases observed in Estonia and Latvia are sustained. However a decrease in the trends of MDR-TB among re-treated cases is starting to appear in this region.

Conclusions

This data demonstrates that most countries of the EU and EEA/EFTA have continued to experience a steady decrease in the overall TB notification rate over the last few decades, even if this trend was briefly reversed in certain countries in the early 1990s. Several epidemiological indicators, such as age distribution, notifications of paediatric TB cases and paediatric TB meningitis trends suggest that the downward trend is real and sustained over the past five years. Additionally, TB mortality rates remain comparatively low.

However this picture should be interpreted with caution. It does not mean that TB is no longer a threat in this part of the world. A number of epidemiological challenges still exist and need to be addressed:

- Within the heterogeneous epidemiological setting described, the number of high/intermediate TB incidence countries remained the same. Serious attention to the evolution of the TB epidemic in these countries is needed.
- The quality of treatment monitoring and reporting remains quite poor and could hamper the effectiveness of TB control.
- Low incidence countries are experiencing a shift of the epidemic towards more vulnerable populations, particularly foreign-born.
- The quality of drug resistance testing and reporting needs to be assessed and further improved. As rates decline, the contribution of drug resistance in slowing down the declining trend of the epidemic will become increasingly important.

Table 2

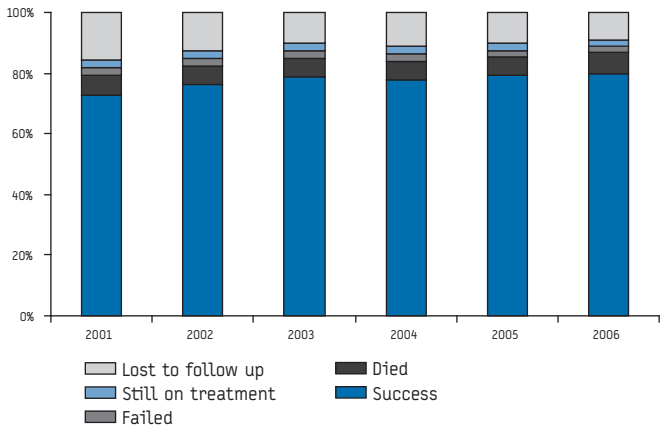
Characteristics of tuberculosis data in EU & EFTA/EEA, 2007

	EU & EFTA/EEA	
	N[b]	
Total population (millions)	30	496.3
Demographic and clinical features of TB cases, 2007		
Total number of cases	30	84917
TB cases / 100000 population	30	16.9
Mean annual % change in notification rate (2003-2007)	30	-3.8%
Foreign origin	30	21%
Sex ratio (male to female), nationals	30	2.0
Sex ratio (male to female), foreign born / citizens	30	1.4
Age over 64 years, nationals	30	21%
Age over 64 years, foreign born / citizens	30	9%
Pulmonary disease	30	80%
Pulmonary sputum smear-positive cases / 100000 population	30	6.7
Previously untreated (diagnosed) for TB	30	79%
Culture positive	30	45%
HIV infection among TB cases (latest available data 2003-2007)	20	2.6%
TB deaths / 100000 (median, latest available rates 2002-2006)	26	0.9
Multidrug resistance (MDR), 2006[c]		
Primary MDR (median)	19	1.5%
Nationals, combined MDR (median)	21	0.6%
Foreign-born/citizens, combined MDR (median)	20	3.9%
Outcome, new definite pulmonary cases, 2005[c,d]		
Success (cure or treatment completion)	21	80%
Death	21	7%
Failure	21	2%
Still on treatment	21	2%
Loss to follow-up (default, transfer, unknown)	21	9%

[a] Mean value unless otherwise indicated; for definition of geographic areas see Technical Note
[b] Number of countries with available data and included in the statistics. Liechtenstein is included in the report, but is only presented as EEA/EFTA country (it does not belong to WHO European Region)
[c] Including only countries with complete/representative nationwide data (see Technical Note)
[d] Among culture positive pulmonary cases in 21 EU/EEA/EFTA countries; in other countries defined by smear or combination of smear and culture
Primary MDR: among previously untreated cases; Combined MDR: among all cases tested (see Technical Note)

Figure 2

Treatment outcome in previously untreated laboratory confirmed pulmonary cases, EU and EFTA/EEA countries 2001 – 2006



Data source: country reports from: Austria, Belgium, Cyprus, Czech Republic, Denmark, Estonia, Germany, Hungary, Iceland, Ireland, Latvia, Lithuania, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia and United Kingdom

- Certain epidemiological and surveillance patterns in selected countries need to be evaluated in more detail. This would include further assessment of sustained increases in paediatric cases and/or overall notifications.

Finally, the trend suggesting a slow but sustained decline in the TB epidemic in the EU, highlights the need to identify a valid impact target to assess the epidemiological progress of the TB prevention and control work.

Outcome and impact indicators for Global TB control are well defined and supported by the existence of the Millennium Development Goals for TB and the Stop TB Partnership Targets. However this framework for measuring quantitative progress towards elimination of tuberculosis at a global level has not proven to be an effective stimulus in low/intermediate incidence settings [1]. Additionally some intermediate/high incidence countries will find it very hard to achieve these targets as they have experienced increasing rates since 1990. The current definition of TB elimination within a population is an incidence rate of less than 1 case per million population per year. This is different when compared with other infectious diseases, where elimination is defined as the lack of active transmission within a population, a definition that more accurately indicates the ability to prevent disease from spreading in a given population [2]. It has, however, been argued that it might be unrealistic to apply such a definition for TB elimination.

This discussion is unlikely to meet expert consensus in the near future. However, the wealth of quality epidemiological information being collected should be carefully analysed and monitored to better understand and predict the direction of the TB epidemic in the EU & EEA/EFTA setting.

Finally it should be remarked that the threat of drug resistance remains ever real. Progress made by the Baltic States in dealing with this problem may provide an example that can be of use for countries outside the EU to study and adopt in such forum as the forthcoming WHO ministerial meeting in Beijing [3].

*Countries of the WHO European Region: Andorra, Albania, Armenia, Austria, Azerbaidjan, Belarus, Belgium, Bosnia & Herzegovina, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Georgia, Germany, Greece, Hungary, Iceland, Ireland, Israel, Italy, Kazakhstan, Kyrgyzstan, Latvia, Lithuania, Luxembourg, Macedonia FYR, Malta, Moldova, Republic of, Monaco, Montenegro, Netherlands, Norway, Poland, Portugal, Romania, Russian Federation, San Marino, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Tajikistan, Turkey, Turkmenistan, Ukraine, United Kingdom and Uzbekistan.

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Marked decrease in reporting incidence of salmonellosis driven by lower rates of Salmonella Enteritidis infections in Germany in 2008 – a continuing trend

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In Germany, since the enactment of the Protection Against Infection Act (IfSG) in 2001, notification of cases of salmonellosis is based on a stable case definition [1], facilitating comparability of data. The annual incidence of notified cases of salmonellosis has declined from over 90 per 100,000 population in 2001 to 60-70 per 100,000 in 2004 through 2007. After very little change from 2005 through 2007, a marked decrease of the number of notified cases (22.6% compared to 2007) was observed in 2008. This drop, as well as the overall decline since 2001 was almost entirely due to the dwindling number of notifications of infections with *Salmonella enterica* subsp. enterica of serotype Enteritidis (SE) (Figure 1).

After a small upsurge in 2007 when large institutional SE outbreaks occurred in Germany, especially in the second and third quarter of the year [2-4], the 34% drop in the annual incidence of notified SE cases from 2007 to 2008 was rather unexpected.

The secular decrease since 2001 in notified SE incidence of 51% affects all age groups (Figure 2) and is most pronounced in adults 20-39 years old (61%) and least pronounced in the elderly (≥60y) (33%). It is consistent throughout Germany and in all months of the year, with the largest decreases observed in the fourth quarter (data not shown). The number of cases reported in SE outbreaks has declined along with the overall number of cases (52% since 2001), and thus the proportion of outbreak cases remained stable (13 -17% annually).

SE infection is frequently associated with consumption of eggs in which SE is the most commonly found serotype [5,6]. In SE outbreak investigations, foods containing eggs [7,8] are often identified as the source of infection.

From 2001 to 2005 (later data not yet available) egg consumption in Germany fell by 7.4% [9]. This decline by itself appears insufficient to explain the magnitude of SE decline in humans. However, this coupled with a reduction in risk behaviour (e.g., less frequent consumption of food containing raw or undercooked eggs) or a decrease in SE prevalence in eggs could help explaining the remarkable decrease in the number of human SE infections. Whereas data series on German consumer behaviour regarding eggs are not available, some data of routine monitoring of table

Figure 1

Incidence of notified cases of Salmonella infection by serotype, Germany, 2001-2008 (data as of 23 January, 2009)

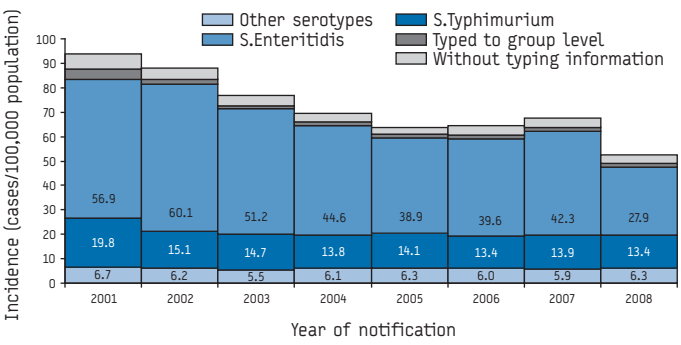
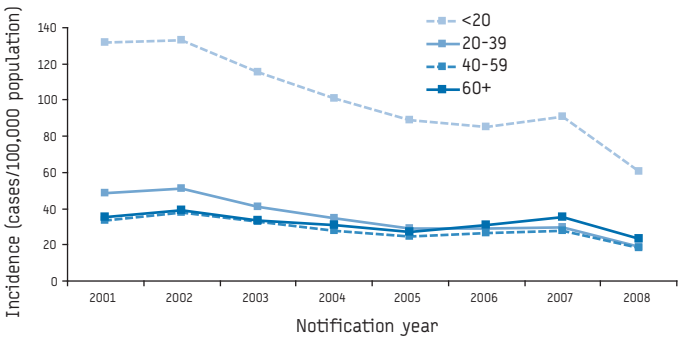


Figure 2

Incidence of notified cases of Salmonella Enteritidis, by age group, Germany, 2001-2008



eggs are. Though the overall prevalence of Salmonella in table eggs shows no downward trend, the decline in human incidence of SE infections in Germany since 2001 does coincide with a reduction of SE prevalence in routine table egg shell samples analysed by food safety authorities in some federal states of Germany (5, 6). Trend analyses indicate that the reduction in SE prevalence in egg shells, falling in these regions from 0.49% in 2001 to 0.19% in 2007 (2008 data not yet available), is statistically significant (e.g. p-value=0.01 in Poisson regression).

A role of reduced consumption of eggs combined with a lower SE prevalence in those eggs would be biologically plausible. However more detailed analyses, including, for example, other food products and phage type information (which is not reportable), need to be conducted to elucidate the mechanisms underlying the reduction in human SE incidence in Germany.

The reported incidence of salmonellosis has been decreasing in many countries of the European Union over the last years [10]. The authors would be interested to know, if this decline in other countries is also driven by falling numbers of SE infections in humans.

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Trends in multidrug-resistant tuberculosis in Scotland, 2000-7

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Overall numbers of multidrug-resistant (MDR) tuberculosis (TB) rose sharply in the United Kingdom and Scotland in 2007. Risk factors associated with MDR TB in the United Kingdom have been identified but there has been no previous report on risk factors associated with MDR TB in Scotland. Enhanced Surveillance of Mycobacterial Infections (ESMI) data were used to examine demographic and clinical characteristics and treatment outcome of MDR TB cases notified in Scotland between 2000-7. There was a total of 11 culture-positive cases of MDR TB, five of which were notified in 2007. The majority of patients were female, 15-44 years old and unemployed. All were born outside the United Kingdom and most had arrived within the past year from or frequently travelled to their home countries in China, the Indian subcontinent or Africa. Except for one individual, our patients did not self report a history of previous diagnosis of TB which was previously identified as a risk factor for MDR TB in the United Kingdom. Only three patients received directly observed treatment (DOT). Only two patients had completed treatment at 12 months, partially due to the inadequate length of follow-up under the current ESMI system. Our results suggest that most patients had primary resistance due to transmission of MDR TB in high incidence countries and thus point to the importance of international efforts to control MDR TB in these countries. In Scotland, national efforts should be made to increase the number of MDR TB patients receiving DOT and to extend follow-up to improve monitoring of treatment outcome. It is important to identify high risk groups for MDR TB infection in order to deliver effective community-based disease control measures.

Introduction

There are an estimated nine million new cases of tuberculosis (TB) worldwide each year and 5.3% of these are multidrug-resistant (MDR) [1]. In 2007, the highest incidence rates for MDR TB ever recorded were detected in 14 countries which comprised China and countries that were members of the former Soviet Union [1]. In the United Kingdom the proportions of MDR TB currently remain low at 1.2% and have been stable since 2000 [2]. However, the number of MDR TB cases per year has increased from 28 in 2000 to 55 in 2007 [2]. This rise is important in terms of future public health planning and resource allocation. It is important to prevent the transmission and emergence of MDR TB because the second line antibiotics that are necessary for treatment are less effective, have toxic side effects and require extended treatment regimes for 18-24 months [3-5]. Treatment failure is therefore more common and subsequently leads to higher mortality rates and relapse [6-7]. It may also result in the emergence of extensively drug-resistant TB (XDR TB). Furthermore, due to increased drug, inpatient and directly observed therapy (DOT) costs, treatment of MDR TB is ten times more expensive than treatment of drug-sensitive TB. In the UK, the management of an MDR TB case has been estimated to cost the NHS £60,000 compared to £6,040 for a patient with drug-sensitive TB [8].

Effective community-based disease control measures, including contact tracing and optimal treatment outcome, rely on identification of patient groups at risk from MDR TB infection. For the United Kingdom specific risk factors associated with MDR TB include being male [9-10], although in 2008, more MDR TB patients were female [2], being 15-44 years old, or of younger age [2, 9-11], being born outside the United Kingdom [2, 10-12], having a history of previous diagnosis of TB [2, 9-13] and being of Black African, Indian-Pakistani-Bangladeshi or Chinese ethnicity [11]. Being HIV positive and living in London were associated with primary resistance [9-10, 12] whereas pulmonary disease and smear positivity were associated with secondary resistance [10, 12].

There has been no previous report on the risk factors associated with MDR TB in Scotland. The Enhanced Surveillance for Mycobacterial Infections (ESMI) scheme was introduced in 2000 by Health Protection Scotland as the routine surveillance system for the collection of demographic, clinical and laboratory data on patients notified with TB in Scotland. We have used data from the ESMI scheme to examine the demographic and clinical characteristics and treatment outcome of MDR TB cases notified in Scotland between 2000-7.

Methods

The Scottish Mycobacteria Reference Laboratory (SMRL) provided data on mycobacterial strains and drug resistance profiles of isolates obtained through culture and antibiotic susceptibility testing. An MDR TB case was defined as a culture positive case of Mycobacterium tuberculosis complex resistant to at least isoniazid and rifampicin. ESMI data were used to calculate the proportions

of TB cases that were MDR TB, over time, with 95% confidence intervals (95% CI) using Wilson's method [14]. Descriptive epidemiology of MDR TB cases, notified between 2000-7 inclusive, was carried out using a case series to examine: sex, age group, country of birth, years since entry into the United Kingdom, travel outside the United Kingdom in the last two years for at least one month, occupation, previous diagnosis of TB (used as a proxy for secondary resistance), pulmonary disease defined as TB infection in the lungs and/or tracheo-bronchial tree, site of disease and whether patients had received DOT. Patients' ethnicity, health board of residence (health boards are the geographical administrative units for the National Health Service in Scotland), sputum positivity for acid fast bacilli (AFB) and additional risk factors such as being immunosuppressed, a refugee/asylum seeker, an excess alcohol user, a drug user, homeless/hostel dweller/rough sleeper or a health care worker were also captured. Treatment outcome and patient status (alive/dead) were recorded 12 months after treatment start date.

Results

There were 2,199 culture confirmed cases of TB in Scotland between 2000-7 and 11 of these (0.5%; 95% CI 0.3-0.9) were MDR TB (Table 1). There were no differences in the numbers of MDR TB cases observed between 2000-6, with a range of 0-2 cases and proportions of 0-0.8%. However, in 2007 the number of cases increased to five which accounted for 1.7% of TB cases, although the increase was not significant due to the small numbers involved.

Demographic data are displayed in Table 2. Information was complete apart from single cases with missing values for number of years since entry into the UK, country travelled to and occupation. The majority of patients were female (8) and 15-44 years old (10). All were born outside the United Kingdom. Countries of birth included China (2), Pakistan (3), India (1), Zimbabwe (2), Somalia (1), Philippines (1) and Eastern Europe (1); ethnicities matched those of the native populations in the countries of origin. Most affected (8) had been resident in the United Kingdom for one year or less and all had been in the United Kingdom for less than five years. Seven had a history of travel abroad for at least one month in the past two years, as recorded by ESMI, and most had travelled to their home countries. The majority were unemployed (7); one of the only two employed patients was a health care worker. As additional risk factors immunosupression was identified for one patient. Between 2000-4 the majority of MDR TB patients (4) were resident in urban areas with large cities which were covered by larger health boards. Smaller health boards covering rural areas have also had MDR TB patients which has impacted on their TB services (data not shown to preserve patients' anonymity).

Clinical data are shown in Table 3. Overall they were complete, apart from pending information regarding treatment outcome in three cases and one case with this information missing. One patient had a history of previous diagnosis of TB and reported having received at least one month of treatment in his home country. Three patients had pulmonary disease and two were also smear-positive. Extra-pulmonary sites of disease included intrathoracic and extrathoracic lymph nodes, pleura and spine. Only three patients were commenced on DOT. After isoniazid and rifampicin, the majority of isolates were resistant to streptomycin (7), rifabutin (7), ethambutol (5), pyrazinamide (4) and clarithromycin (4). Resistance to prothionamide (1) and clofazimine (1) was also detected in two different isolates. Only two patients had completed treatment 12 months after treatment start date. For three patients having started treatment at the end of 2007 information on treatment outcomes were pending. Only one patient died whilst under treatment.

Discussion

In 2007 there were five cases of MDR TB in Scotland and 55 in the UK representing the highest numbers ever recorded across the United Kingdom. The proportion of MDR TB in Scotland which was 1.7%, was higher than the UK national average [2]. However, it remained below the national guideline level of 2%, which was set to indicate adequate MDR TB control in the United Kingdom [15]. The increase in MDR TB cases in 2007 may indicate future trends and emphasizes the importance of maintaining or improving levels of control in high risk populations. The results of our study indicate that MDR TB cases in Scotland are imported into the country by young migrant populations recently arrived or returned from countries with high incidence rates of MDR TB. It is perhaps surprising that only one MDR TB patient was from Eastern Europe considering the recent influx of migrant workers from Eastern Europe into Scotland and the rest of the United Kingdom and the high incidence rates of MDR TB in this region [1]. It takes two to five years for the majority of new migrants, entering the UK with latent TB, to develop an active infection [2] and therefore it is possible that Scotland may experience a delay before detecting an increase in MDR TB patients from Eastern Europe. It is also possible that Eastern European patients from non-EU countries return home to seek health care and are thus not picked up by the United Kingdom notification systems.

MDR TB is often associated with a previous history of treatment [1-2, 16-17] and treatment failures or mismanagement leading to secondary resistance. However, in this case series, only one patient had a previous history of TB and treatment, suggesting that most patients had primary resistance, due to transmission of MDR-TB, in high incidence countries. However, previous history of TB diagnosis and treatment was self-reported, so these data may be biased.

The majority of MDR TB patients in our study had non-pulmonary infections with associated lower risks of transmission. Eight of the eleven patients were on self administered treatment, rather

Table 1

Sputum-positive multidrug-resistant (MDR) tuberculosis (TB) in Scotland, 2000–2007 (n=11)

Year	MDR TB			Total TB sputum-positive cases (n)
	n	%*	(95% CI**)	
2000	0	0	(0.0-1.4)	285
2001	2	0.8	(0.1-2.8)	248
2002	1	0.4	(0.01-2.2)	256
2003	1	0.4	(0.01-2.1)	265
2004	1	0.3	(0.01-1.8)	302
2005	0	0	(0.0-1.3)	270
2006	1	0.4	(0.01-1.9)	282
2007	5	1.7	(0.6-3.9)	291
Total	11	0.5	(0.3-0.9)	2,199

* proportion of total number of TB cases
** 95% confidence intervals (CI)

than on DOT which can aid treatment completion, especially with extended treatment regimes. Partially due to inadequate length of follow-up (12 months) under the current ESMI system, only two patients were recorded as completing treatment 12 months after treatment start date. As MDR TB usually requires treatment for at least 18 months, the recorded treatment completion at 12 months is likely to be an artifact. Both outcome forms for these patients were received with a delay of six months, which suggests that they also took 18 months to complete treatment. In Scotland, it has recently been agreed to introduce further follow-up of TB patients at 24 months, for those individuals who had not completed treatment at 12 months. In order to improve monitoring of MDR TB patients, the Health Protection Agency in England has similarly revised its system to monitor specific patients at 24 months [2].

This study is the first to describe the patterns and characteristics of MDR TB in Scotland. The results point to the importance of international efforts to improve treatment and control of MDR TB transmission in high incidence countries, as addressed by the World Health Organization (WHO) Plan to stop TB in 18 High-Priority countries in the WHO European region [3]. This is essential not only to alleviate the associated morbidity and mortality in these countries, but also to prevent the spread of resistant TB strains to low incidence countries, which could impede all future hopes of global control of tuberculosis. National efforts should be made to encourage all new entrants to Scotland to register with general medical practices as soon as possible and research is being carried out to identify incentives which may help to increase NHS registration in these populations [18]. Clinicians should suspect MDR in TB patients from all regions of the world with a high incidence of MDR TB and should ensure timely susceptibility testing is carried out on isolates, that appropriate drug regimes are prescribed and contact tracing is carried out as required following appropriate guidance, including guidance on long haul air travel.

Table 2

Demographic characteristics of multidrug-resistant (MDR) tuberculosis (TB) cases in Scotland, 2000-2007 (n=11)

Patient	Year	Sex	Age group	UK born	Country of origin	Years since entry into the UK	Significant travel outside the UK	Occupation
1	2001	M	15-44	No	China	<1	Home country	Unemployed
2	2001	M	15-44	No	Pakistan	4	Unknown	Unemployed
3	2002	F	15-44	No	Pakistan	1	Home country	Unemployed
4	2003	F	45-65	No	Zimbabwe	<1	Home country	Health care worker
5	2004	F	15-44	No	Philippines	<1	Western Europe	Unemployed
6	2006	F	15-44	No	Zimbabwe	1	Home country	Unknown
7	2007	F	15-44	No	India	2	No	Employed
8	2007	F	15-44	No	Somalia	1	No	Unemployed
9	2007	F	15-44	No	Eastern Europe	<1	Unknown country	Unemployed
10	2007	M	15-44	No	Pakistan	Unknown	Home country	Unemployed
11	2007	F	15-44	No	China	<1	No	Further Education

M=Male, F=Female

Table 3

Clinical characteristics and treatment outcomes of multidrug-resistant (MDR) tuberculosis (TB) cases in Scotland, 2000-2007 (n=11)

Patient	Previous diagnosis	Pulmonary TB	Site of disease	Follow up at 12 months	DOT	Alive	Resistance
1	Yes	Yes	Lung	Still on treatment	Yes	Yes	INH,RMP,STM,RFB,CLR
2	No	No	Cervical LN	Treatment completed	Yes	Yes	INH,RMP,EMB,RFB,CLR
3	No	Yes	Lung	Missing	Yes	Yes	INH,RMP,EMB,PZA,STM
4	No	No	Axillary LN	Still on treatment	No	Yes	INH,RMP,EMB,RFB
5	No	No	Cervical LN	Still on treatment	No	Yes	INH,RMP,RFB,PTH
6	No	No	ITH and cervical LN's	Treatment completed	No	Yes	INH,RMP,EMB,PZA,STM
7	No	No	ITH, abdominal LN's, spine	Still on treatment	No	No	INH,RMP,EMB,RFB,CLR
8	No	No	Supraclavicular LN	Still on treatment	No	Yes	INH,RMP,PZA,STM,RFB,CFZ
9	No	No	Pleural	Pending	No	Pending	INH,RMP,PZA,STM,RFB
10	No	No	Spine	Pending	No	Pending	INH,RMP,STM
11	No	Yes	Lung	Pending	No	Pending	INH,RMP,STM, RFB,CLR

Key: INH=Isoniazid, RMP=Rifampicin, EMB=Ethambutol, PZA=Pyrazinamide, STM=Streptomycin, RFB=Rifabutin, CLR=Clarithromycin, CFZ=Clofazimine, PTH=Prothionamide, ITH=Intrathoracic and LN=lymph node.

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Substantial underreporting of tuberculosis in West Greece - implications for local and national surveillance

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In order to estimate the reliability of the officially reported national tuberculosis (TB) incidence rates we performed a retrospective review of data collected in regional and national public health framework. TB notifications for the period 2000-2003 were obtained from two major hospitals and three relevant Public Health Departments (PHDs) in the region of West Greece, and subsequently compared with the data reported to the Hellenic Centre for Diseases Control (KEELPNO). During the four-year study period a total of 161 cases of TB were reported to the PHDs in West Greece; 70% of these cases were reported to the KEELPNO. Furthermore only 72 (38.7%) out of the 186 cases of TB identified in the two hospitals were notified to the PHDs. Assuming that the degree of undernotification observed for the two hospitals is the same throughout the region, we estimated that the case detection rate was 14 cases per 100,000 persons per year, i.e. 3.7 times higher than the rate officially reported for the period 2000-2003. Male predominance (2.1, male/female ratio) and an increased incidence in the elders (older than 60 years) and adolescents (10-14 years old) were also evident. The study demonstrated a substantial underestimation of TB burden in West Greece. In the face of the massive influx of immigrants and refugees coming from regions with high TB incidence and the increase of the number of drug-resistant cases a reliable and complete notification of TB is crucial in the planning of programs and development of appropriate control policies.

Introduction

The subject of underreporting is an important problem in tuberculosis (TB) care in many countries in the world including Europe. It is particularly important for Greece as its case detection rate, according to the World Health Organization (WHO) data, is one of the lowest in Europe [1,2]. In Greece as well as in other European countries the burden of disease is increasingly associated with immigrants from countries with a high prevalence of tuberculosis and other groups at higher risk of infection, such as the elderly (aged 60 years and older), homeless, drug users, and immunosuppressed patients [3,4]. It is widely acknowledged that these high risk groups should be the target of prevention and control strategies of tuberculosis in the European Union (EU) [5].

In Greece, during the period 1996-2005, the notification rates ranged between 5 and 11 cases per 100,000 population per year [6]. Between 2000 and 2003 only 5-6 cases per 100,000 population were reported annually through the national notification system, resulting in one of the lowest rates in the EU, comparable only with Sweden, Malta and Cyprus. It is worth mentioning that in the same period neighbouring countries reported notification rates between 19.3 (Albania) and 43.8 (Bulgaria) [6]. However, the Greek national data are not considered as complete due to various limitations in the notification system [7]. The massive influx of immigrants from the Balkans, Eastern Europe and Asia, i.e. regions with high TB incidence and increase in resistance of Mycobacterium tuberculosis does not correspond with the reported case detection rate [8-10]. Therefore, the necessity to report exhaustive and representative data in order to obtain reliable comparisons has been widely acknowledged not only in Greece [5].

TB has been a notifiable disease for many years, but completeness of notification varies among different countries. Despite a number of limitations, notification contributes to the monitoring and control of TB. The main drawbacks are insufficient data and incompleteness of notification which do not reflect the actual situation in the population [2,11,12,13]. In Greece, reporting of TB is obligatory and physicians make notification on a standardised notification form. TB cases are notifiable if they meet certain criteria: TB cases with culture-confirmed disease due to M. tuberculosis or culture-negative TB cases with clinical and/or radiological signs and/or symptoms treated with antituberculosis drugs [14]. At the level of the prefectures, the Public Health Departments (PHDs) are charged with the collection of data regarding all notifiable diseases. At the national level, the Hellenic Centre for Disease Control (KEELPNO) collects information from all PHDs for central epidemiological surveillance and trend analysis purposes.

The objective of this study was to examine the process of reporting TB cases between the local (two major hospitals) and regional levels (three public health departments) and subsequently between the regional and national levels (KEELPNO) in order to

evaluate the completeness of notification records held at the national level for the region of West Greece.

Study population and methods

The study took place in West Greece, one of the 13 peripheries of Greece, which is further divided into the prefectures of Aitoloakarnania, Achaia and Elia, and covers an area of 11,350 square kilometres (8.6% of the total area of Greece). According to the 2001 census, the population of this region was 741,282 (7% of the country's total population).

For the study period of 2000-2003, the data on TB notifications were obtained both from the three prefectural PHDs and from the KEELPNO.

For the same period, all clinical records on TB cases were collected from the two major tertiary care hospitals in the municipality of Achaia (the Specialised Hospital for Pulmonary Diseases – Thorax Hospital and the University Hospital of Patras). Although in West Greece there are nine more small and medium-sized hospitals as well as 17 health centres, the two hospitals selected for the study are believed to cover a large proportion of TB cases in this region. For each TB patient, data were obtained regarding the date of diagnosis, the site of disease, the criteria used for the case's ascertainment and demographic characteristics (sex, age, profession, place of residence). These data were obtained mainly through the records kept by the hospital-based Committee of Infectious Disease Control which is responsible by law for the continuous monitoring of all communicable diseases. In the next step, two researchers collected and confirmed all records of TB cases kept in handwritten form in a corresponding book of laboratory results in the Departments of Microbiology and Cytology. Furthermore we have traced additional cases through the patient discharge lists from the departments of internal medicine and pulmonology.

Incidence rates (per 100,000 population) were calculated according to 2001 census provided by the National Statistical Service of Greece. The study was approved by both the Board of Medical School of the University of Patras and the Regional Health Authority of West Greece.

Statistical Package for Social Sciences (SPSS) program-version 12.0 (SPSS Inc., USA) was used for data entry and descriptive analysis.

Results

Table 1 shows the TB cases documented in the two selected hospitals and the corresponding notifications to the PHDs. Based on the place of residence in West Greece, 186 notifiable TB cases were identified in the two hospitals in the four-year period. Of these, only 72 cases (38.7%) were reported to the PHDs. Specifically from the 144 TB cases identified in the Thorax-Hospital only 43 (30%) were reported to the corresponding PHDs whereas the notification rate for the University Hospital was significantly higher (69%). Consequently, at least 114 cases of TB were not notified to the PHDs of West Greece during 2000-2003, i.e. almost 30 cases per year. The combined undernotification rate of the two hospitals reached 61% (114/186) and it was significantly higher in 2002 and 2003 compared to 2000 and 2001.

During the study period (2000-2003), 161 cases were reported to the PHDs in West Greece by all sources (including 72 cases notified by the two hospitals), so that in total we identified 275 TB cases which would correspond to a mean annual notification rate of 9.5 per 100,000 (Figure). On the basis of demographical characteristics of the study population we observed a clear predominance of male patients (male/female ratio of 2.1) and an increased incidence in the elderly (over 60 years old) as well

Table 1

Tuberculosis cases documented and reported to the Public Health Departments by two large hospitals in West Greece during 2000-2003

Prefecture	Thorax and University Hospital identified cases	Reported cases to PHD	Notification rate (%)
Achaia	100	22	22
Aitoloakarnania	39	20	51.3
Ilia	47	30	63.8
West Greece total	186	72	38.7

Figure

Mean notification rate of tuberculosis per 100,000 population, Greece, 2000-2003, by age and sex

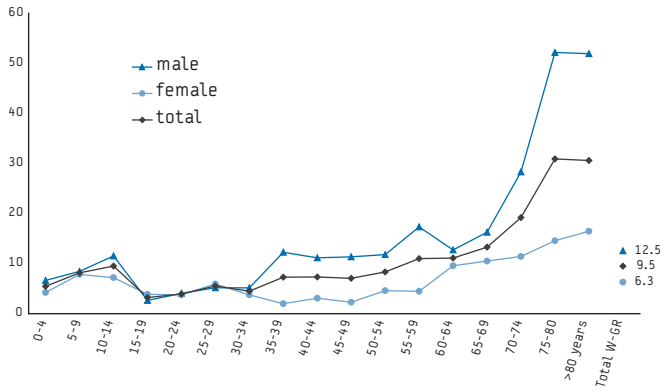

Table 2

Cases of tuberculosis registered in the Public Health Departments in three prefectures of West Greece and reported to the Hellenic Centre for Infectious Disease Control (KEELPNO)

Year	Registered cases of TB					
	Public Health Departments				Reported to KEELPNO	
	Achaia	Aitoloa-karnania	Ilia	West Greece total	From West Greece n (%)	Greece total
2000	12	26	23	61	56 (92%)	703
2001	7	4	9	20	18 (90%)	617
2002	18	13	10	41	27 (66%)	581
2003	13	12	14	39	12 (31%)	621
Total	50	55	56	161	113 (70%)	2,522

as a clustering in the age-group of 10-14 years old (Figure). It is worth mentioning that eight paediatric cases of TB, including six boys and a girl from the urban area of Achaia, were reported from February to May 2002. Any other information was not possible to be obtained for these cases.

Finally, only 70% of the 161 cases notified to the three PHDs were further reported by the PHDs to the KEELPNO (Table 2). There were no significant differences in the proportion of cases reported from the PHDs to KEELPNO by prefecture, since the range was 68-74%.

Discussion

This study demonstrates a substantial underestimation of TB burden in West Greece and reflects an insufficient TB monitoring system in Greece. Assuming that the degree of undernotification observed is the same throughout the whole region of West Greece – which is more than probable considering that the Infectious Diseases Control Committees of the two large hospitals are relatively well organised – we estimate that the actual case detection rate could reach 14 cases per 100,000 persons per year, i.e. a value 3.7 times higher than the data officially reported by the KEELPNO for the period 2000-03. The reasons for this underreporting are not well studied. Although our results cannot necessarily be extrapolated to the whole national surveillance system, the few studies on completeness of tuberculosis notification in Greece have shown similar results [7,15,16]. Obviously the participation of physicians (in both primary and hospital care) in the obligatory (passive) reporting system is not efficient [17] perhaps because the reporting system has not been properly introduced to health professionals and other related stakeholders, and the forms as well as the procedures of reporting remain very complicated. As other studies mentioned, the inconsistency or incompleteness of data produce further difficulties in the data analysis [13,14,18].

A great challenge for TB control is posed by the fact that during the last decade there has been an uncontrolled illegal immigration from high TB endemic regions such as Balkans, Eastern Europe and Asia in many European countries including Greece. Between 1991 and 2004, the number of immigrants in Greece has raised from 270,000 to 1.1 million, accounting for the 10.3% of the total population. Immigrant population densities ranged between 0 and 25% in different areas, whereas in West Greece the density lies around the mean. Immigrants originated mainly from Albania (55%), Bulgaria (4.7%), Georgia (2.9%), Romania (2.2%), Russia (2.3%), Ukraine (1.9%), Poland (1.9%) and Asia (5.6%, mainly Pakistan, India, Iraq, Syria etc.) [8]. During the study period, many of the abovementioned countries showed very high mean annual TB incidence rates per 100,000 population, like Romania (140), Georgia (133), Russia (97), Ukraine (78), Bulgaria (44) [6]. The majority of these (in a great part illegal) immigrants and refugees usually do not undergo any tuberculosis control program [19,20]. Possible cases among the immigrants are less likely to be diagnosed which consequently contribute to further underestimation of the disease burden and facilitate further spread of TB in the country [16,19,20,21].

Another important finding is the observed peak in adolescents and the gender differences. This result is in line with well-established knowledge. During adolescence, higher prevalence of TB among males has been reported which may reflect a genuine sex difference in susceptibility to TB infection [22,23]. It is probable that our results reflect the usual biphasic age-related TB incidence curve often found in low-incidence countries: the first peak mainly attributable to recent transmission and disease among young immigrants and the second peak reflecting reactivation of old infections among the native population in Western European countries [2,6]. Another possibility could be that undernotification is lesser in paediatric cases than in adult cases. However, the first peak in our curve is in a younger age group than in some other countries and cannot be explained by immigrant labour or marriage (usually 20–40 years age groups) [2,6]. Perhaps the peak in adolescents is due to a school outbreak but we lack data to support that. Gender differences in biological susceptibility may be one plausible reason but also socio-economic and cultural factors may play a role in determining sex differences in rates of infection and progression to disease. Also differences in the risk of exposure to infection between male and female adolescents play a role.

Our results indicate that in two specialised hospitals in West Greece physicians seem reluctant to notify TB cases and, in addition, the regional responsible authorities (PHDs) seem to fail in executing their professional duty of forwarding all surveillance data to the national level. This is partly due to delays in collecting all necessary supplementary administrative data from the hospitals which cause further delays in forwarding on time the data to KEELPNO. These problems should be investigated and addressed by, for example, the Ministry of Health or the Health Care Inspectorate. Effective disease control and prevention in Greece can be achieved only with a well organised surveillance of TB at the local, regional and national level in order to evaluate and plan programs, to target resources and to develop appropriate policies. In order to improve the accuracy of the notification system good understanding of the reasons for underreporting and proper and sincere cooperation with the physicians, the health centres and the hospitals are required. In the light of our findings, the following recommendations are made to increase the notification of TB and to target disadvantaged groups. On the national level KEELPNO must inform regularly all PHDs and physicians regarding the importance and usefulness of the TB notification as well as of the notifications for other infectious diseases. National training and consensus meetings should be organized in order to improve notification rates. On the regional level all necessary activities regarding notification should be centralized and coordinated by the local PHDs, given that offices and professionals at the local PHDs have to perform their duties. The quantity of information collected and reported must balance the need for simplicity, increased efficiency of the system and sufficient data. Cooperation should be strengthened among PHDs, health professionals and KEELPNO. Medical examination of immigrants (especially from countries with high TB incidence) should be enforced.

In the face of the massive influx of immigrants and refugees coming from regions with high TB incidence and the increase of the number of drug-resistant cases challenging the quality of the TB control system a reliable and complete notification of TB – including drug susceptibility testing for monitoring the occurrence of drug-resistant TB – is crucial in the planning of programs and development of appropriate control policies regarding early case finding and transmission control as well as treatment adherence and success.

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Effectiveness of tuberculosis contact tracing among migrants and the foreign-born population

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A literature review was performed to assess the effectiveness of tuberculosis (TB) contact tracing among migrants and the foreign-born population with emphasis on the European Union. Effectiveness of contact tracing was assessed using the following indicators: coverage, proportion of contacts with TB (TB yield), proportion of contacts with latent tuberculosis infection (LTBI yield) and number of investigated contacts per index case (contacts/index case ratio). The key findings from the literature review were: Among foreign-born contacts, a higher median LTBI yield was found compared with contacts born in the country, when exposed to the same foreign-born index cases. No clear differences were observed between TB and LTBI yield among contacts of foreign-born index cases compared with contacts of index cases from the general population (including the foreign-born) due to the large variation seen between the studies. The included non-European studies screened more contacts per foreign-born index case, used lower cut-off values to define a positive tuberculosis skin test and found higher LTBI yields among contacts. Although the high heterogeneity across the studies made the comparison challenging, several conclusions are made regarding contact tracing among migrants.

Introduction

Contact tracing is regarded as an effective strategy to identify recently infected individuals and has become an essential component of the tuberculosis (TB) control strategy in most low-incidence countries [1-4].

In most European countries, migrants and foreign-born account for a large proportion of TB patients, ranging from 9% to 76% [5]. Their risk of infection and progression to disease might differ from the local-born population (for the purpose of this paper, the term 'local-born' will be used in the sense of 'born in the country') due to increased exposure to TB in their country of origin [6]. Diagnostic results may need to be interpreted differently among migrants due to the high level of people in this group who are vaccinated with Bacillus Calmette-Guérin (BCG) and to the high prevalence of latent tuberculosis infection (LTBI) [6]. Some countries with a high prevalence of tuberculosis also have a high prevalence of human immunodeficiency virus (HIV) and high co-infection rates. Diagnosis of both latent TB infection and active TB are more complicated in this population. Particularly, interpretation of the results of the tuberculosis skin test (TST) is often made difficult due to the high number of false negative results.

Regardless of the strategy used to detect TB and LTBI among migrants, it needs to be effective in the group that is targeted. Underwood et al. compared contact tracing with new entrant screening in East London and concluded that contact tracing was more effective in detecting and preventing tuberculosis than new entrant screening, mainly because contact tracing selects for families or communities at particularly high risk [7].

The above issues need careful evaluation when performing contact tracing among the migrants and foreign-born.

Contact tracing in general serves different purposes [4]:

- Identifying individuals with TB disease or LTBI among the contacts of a TB patient and providing adequate treatment or follow-up;
- Reducing morbidity and mortality due to TB among newly infected individuals;
- Reducing further transmission.
- The objective of this review is to assess the effectiveness of TB contact tracing among migrants and the foreign-born population, hereafter referred to as foreign-born, with emphasis on the European Union (EU).

Methods

Literature search

The online reference databases PubMed and Cochrane were searched using keywords combinations of TUBERCUL(OSIS) and IMMIGRANT(S) (or MIGRANT(S) or ASYLUM SEEKER(S) or REFUGEE(S) or FOREIGN-BORN or NEW ENTRANTS) and CONTACT (TRACING or INVESTIGATION or EXAMINATION). The search was limited to publications in English from the last 10 years. Additional references were obtained via the reference lists of the articles found through the search engines. Articles published up to June 2008 were included. Titles and abstracts were screened to sort the relevant papers from the non-relevant ones. Abstracts and where available full text of relevant papers were thoroughly screened and classified as A, B, C or D:

A: Randomised comparative research, where intervention and control are randomly assigned to receive a certain screening programme/test;

B: Studies reporting yield and/or coverage of contact tracing among the foreign-born by any given strategy (i.e. stone-in-the-pond principle, workplace contacts only) or any given method (chest X-ray (CXR), tuberculin skin test (TST), interferon gamma release assays (IGRA), symptom screening);

C: Studies reporting on contact tracing among the foreign-born but not reporting yield or coverage data;

D: Studies discussing policies and strategies of contact tracing at country or regional level in relation to public health/epidemiology as well as studies on the cost-effectiveness of contact tracing. Studies that reported contact tracing but did not relate to foreign-born people were also included in this group.

This classification was adapted for contact tracing studies from the classification used by Klinkenberg et al. for studies into the effectiveness of TB screening strategies for migrants [8].

Data Extraction

A datasheet was designed to extract data from articles classified A and B. We did not attempt to obtain original data. Articles classified C and D were used for discussion of the findings. In some studies, no differentiation was made between foreign-born and local-born index cases and therefore the term "index cases from the general population" was used.

Definitions

Index case: the initial patient diagnosed with TB.

Contact: a person who may have been exposed to the index case during the infectious phase.

LTBI yield: the proportion of LTBI cases detected among the total number of fully investigated contacts.

TB yield: the proportion of TB cases detected among the total number of fully investigated contacts.

Coverage: the proportion of investigated contacts (for LTBI) relative to the total number of listed contacts.

Contacts/index case ratio: the number of fully investigated contacts (for LTBI and TB) per index case.

LTBI treatment rate: the proportion of infected contacts that started LTBI treatment relative to the total number of eligible infected contacts.

LTBI treatment completion rate: proportion of contacts that completed LTBI treatment relative to the total number of infected contacts that started LTBI treatment.

Stone-in-the-pond or ring principle: a strategy wherein contacts are indentified in concentric circles around the index case, depending on the frequency and intimacy of their contact [9].

Definitions for the expressions *migrant, asylum seeker, foreign-born and illegal migrant* were adapted from Rieder *et al*. [10].

Definitions of closeness of contacts where adapted from Kamphorst *et al.* [4].

Effectiveness of contact tracing

The following indicators, based on recommendations by the United States Centers for Disease Control and Prevention (CDC) in 2005, were used to assess the effectiveness of contact tracing [11]: coverage, TB yield, LTBI yield and contacts/index case ratio. The higher the values of these indicators, the more effective they were considered to be. For the sake of consistency the different indicators were recalculated where possible using the same definition across all studies.

Because the strategy and the context of contact tracing across the studies differed considerably (depending on setting, infectiousness of the index case, media interest etc.), five analytical approaches were identified and followed:

1. Assessment of studies describing contact tracing for one foreign-born index case.
2. Assessment of studies reporting pooled results of smaller contact investigations exercises. For these studies, outcomes for foreign-born index cases were compared with outcomes for index cases from the general population (including foreign-born index cases) to assess differences in outcomes.
3. Assessment of differences in transmission of TB infection from foreign-born index cases to foreign-born contacts and local-born contacts.
4. Evaluation of whether the closeness of contacts affected the effectiveness of contact tracing.
5. Comparison between European and non-European studies with regards to the effectiveness of contact tracing.

Because only few studies reported yield among contacts by sputum status of the index case, data were not sufficient to present stratified results for this.

The results of three contact investigations described by Kim et al. were pooled to be included under approach 2, as all three were large scale investigations in a similar setting using a comparable strategy [12].

Results

Literature search

A total of 112 (non-duplicate) references were found using the search terms. A further six studies were found via the references of relevant articles. In addition, one study was found when PubMed was searched for studies not written in English, making it a total of 119 studies. After thorough screening of abstract and, where available, full paper, 70 papers were considered relevant and given a classification of A, B, C or D. No papers were classified as category A. Eighteen papers were classified B, of which six were from EU countries [13-18] and twelve from non-EU countries [12,19-29]. Table 1 provides an overview of the key parameters extracted from the eighteen B-classified studies.

Contact tracing strategies

No uniform contact tracing strategy was used across the selected studies. In six studies, the stone-in-the-pond principle was used

Table 1

Overview of contacts/index case ratio, coverage, TB yield and LTBI yield reported in the 18 B-classified studies

Parameter	Proportion (interquartile range) [range]
No. of papers	18
Contacts/index case ratio	7.5 (4.4–71.5) [3.0–475]
Coverage	73.5% (39.3–82.3) [29.1–93.3]
TB yield	0.44% (0.00–2.15) [0.00–14.08]
LTBI yield	31.9% (16.9–36.9) [0.0–44.4]
LTBI treatment started	83.1% (72.9–94.6) [69.1–100]
LTBI treatment completed	63.6% (56.4–67.2) [43.5–78.6]

[14,16-19,21]. In three studies, only workplace contacts were investigated. In the study by Gulati et al., the workplace contact investigation consisted of four components [22]: 1) interview with the index case; 2) a qualitative evaluation of the buildings and their ventilation systems; 3) screening of the co-workers; and 4) interviews with co-workers. The other two studies focused on workplace contacts because the index cases were foreign-born healthcare workers [13,26]. In two studies, only close contacts were screened [24,27] and in one study only household contacts [20]. In the remaining six studies, the contact tracing strategy was not clearly described, mainly because these were retrospective studies that used pooled data of various contact investigations.

With regard to the five analytical approaches described in the methods section, the following was found:

1. Studies with one index case of active tuberculosis

Five studies reported contact tracing activities around one foreign-born index case (Table 2). The median TB yield reported was 0.0% (interquartile range (IQR) 0.0–3.52). The median LTBI yield reported was 28.9% (IQR 12.7–37.1). A median of 89.2% (IQR 81.3–94.8) of the eligible LTBI identified contacts started preventive treatment, of whom a median of 66.7% (IQR 55.1–72.6) completed the preventive treatment.

2. Studies with pooled results of contact investigations

In Table 3, studies with pooled results of different contact investigations are presented.

TB yields among contacts of exclusively foreign-born index cases were in the same range as among contacts of index cases from the general population (median TB yield of 0.63% (IQR 0.5–1.3%) versus 0.46% (IQR 0.0–2.2%)) The median LTBI yield seemed slightly higher among contacts of foreign-born index cases compared with contacts of index cases from the general population, being 39.1% (IQR 20.6–43.7%) and 33.7% (IQR 28.5–36.2%), respectively.

3. Foreign-born and local-born contacts from the same index case

Four studies reported separately on LTBI (but not TB disease) detected among foreign-born contacts and local-born contacts, with both groups exposed to the same foreign-born index cases (Table 4). The LTBI yield among foreign-born contacts was notably higher than among local-born contacts (median 48.9% versus 12.1%) except in one study: Verver et al. reported a slightly higher LTBI yield among local-born contacts than among foreign-born contacts [17]. The contacts/index case ratio found in foreign-born contacts and local-born contacts in these studies was similar (medians of 44.0 and 43.0, respectively).

4. Yield in close contacts and non-close contacts

The effect of closeness of contacts was assessed by comparing findings among close and non-close contacts from foreign-born index cases and index cases from the general population (Table 5).

The results indicate a slightly higher median LTBI yield in close contacts of foreign-born index cases than of index cases from the general population (median 43.7% and 37.0%, respectively), although the interquartile ranges are overlapping. In non-close contacts, the median LTBI yield is higher among contacts of index cases from the general population than among contacts of foreign-born index cases (median 29.0% versus 15.4%). However, the

Table 2

Variables of effectiveness in studies reporting contact tracing in studies with one foreign-born index case

Country	Country/region of origin index case	Contacts/ index case ratio (n)	Coverage (%)	TB yield (%)	LTBI yield (%)	Study
The Netherlands	Algeria	n.r.	n.r.	0.00	12.7[a]	[18]
United States	The Philippines	475	29.1	0.00	5.3[b]	[26]
United States	n.r. (foreign-born)	63	n.r.	14.1	44.4[b]	[25]
United States	El Salvador	97	93.3	n.r.	37.1[b]	[22]
United States	Central America	218	82.6	0.00	28.9[b]	[23]
-	-	157.5 (88.5–282.3)	82.6 (55.9–87.9)	0.0 (0.0–3.52)	28.9 (12.7–37.1)	Median (IQR)

IQR= interquartile range; n.r.= not reported.
[a] TST+ was defined as an induration of >10 mm; [b] TST+ was defined as an induration of ≥5 mm.
Note: In one of the five studies, TB yield was not reported as the paper focused on risk factors for LTBI. In three studies, no contacts with TB were detected [18,23,26]. The fourth study found 10 cases among 71 contacts [25].

Table 3

Median with interquartile range of effectiveness indicators for studies with pooled results of contact investigations

No. of studies	Median proportion of index cases that are foreign-born	Contacts/index case ratio (n)	Coverage (%)	TB yield (%)	LTBI yield (%)	References
6	100%	5.7 (4.8–12.3)	79.7 (76.0-81.9)	0.63 (0.48-1.31)	39.1 (20.6-43.7)	[12,14,17,19,21,24]
9	56.0 (51.5-60.0)	5.1 (4.1-6.9)	79.2 (75.3-83.1)	0.46 (0.04-2.15)	33.7 (28.5-36.2)	[13,15,16,20,21,24,27-29]

interquartile ranges are similar. The large difference reported in the contacts/index case ratio between non-close contacts of foreign-born index cases and those derived from index cases from the general population (48.0 and 2.6, respectively) is due to the fact that the data for the first group were mainly obtained in studies reporting on one large contact investigation. The high contacts/index case ratio may also explain the lower LTBI yield found in non-close contacts of foreign-born index cases.

Interestingly, the median TB yield found among close contacts of index cases from the general population was higher than among close contacts of foreign-born index cases (median 2.2% and 0.0%, respectively). However, results should be interpreted with care as only three studies were available of which two had a TB yield of 0.0%. The close contacts included local-born individuals as well as foreign-born individuals, although it is reasonable to assume that a higher proportion of close contacts of foreign-born index cases were themselves foreign-born (e.g. household contacts).

5. EU studies versus non-EU studies

Three EU studies and eight non-EU studies were found which reported specifically on contact tracing among foreign-born index cases. Five of the non-EU studies were reports of a single large contact investigation, which explains the high contacts/index case ratio. In the EU-studies a median LTBI yield of 11.6% (IQR 11.1–12.2%) was found; in non-EU studies it was 38.1% (IQR 26.8–43.9%). This large difference in LTBI yield is likely to be (at least partly) due to the lower TST cut-off values used in the non-EU studies (i.e. a positive TST defined as an induration of ≥5mm). The median TB yield was comparable between EU studies (0.44%, IQR 0.2–1.5%) and non-EU studies (0.60%, IQR 0.0–1.1%).

6. Sputum smear status of the index case

Sixteen of the 18 studies included in this review reported sputum smear status of the index case. However, only six of them compared outcomes by sputum smear status [15-17,24,27,29]. For these, a higher LTBI yield was found among contacts of sputum smear-positive index cases than among smear-negative index cases. An interesting difference regarding smear status was reported by Golub *et al.* [24]. Among contacts of sputum smear-positive index cases, similar LTBI rates were found in contacts of foreign-born and local-born index cases (46% and 43%, respectively). However, for sputum smear-negative index cases there was a difference. Among the contacts of local-born index cases, only 15% were infected, compared to 44% among the contacts of foreign-born index cases.

Discussion

The main findings resulting from this literature review were:

- When exposed to the same foreign-born index cases, a higher median LTBI yield was found among foreign-born contacts compared to local-born contacts.
- Large variation was seen between studies and no differences were observed between TB or LTBI yield among contacts of foreign-born index cases compared with contacts of index cases from the general population (including the foreign-born).

Table 4

The transmission of LTBI: foreign-born index cases to foreign-born contacts and foreign-born index cases to local-born contacts*

Transmission: foreign-born index cases to foreign-born contacts		Transmission: foreign-born index cases to local-born/low prevalence		Study
Contacts/index case ratio (n)	LTBI yield (%)	Contacts/index case ratio (n)	LTBI yield (%)	
2.0	9.7[a]	0.9	12.6	[17]
52.0	67.3[b]	25	44.0	[25]
36.0	80.6[b]	61	11.5	[22]
82.0	30.5[b]	124	8.9	[12]
44.0 (27.5–59.5)	48.9 (25.3–70.6)	43.0 (19.0–76.8)	12.1 (10.8–20.5)	Median (IQR)

IQR=interquartile range.
* The results in both parts of the table are from the same studies; [a] TST+ was defined as an induration of ≥10 mm for non BCG-vaccinated children and an induration of ≥16 mm for BCG-vaccinated children; [b] TST+ was defined as an induration of ≥5 mm; [c] TST+ was defined as an induration of >10 mm.

Table 5

Median with interquartile range of effectiveness indicators for contact tracing in close contacts and non-close contacts in foreign-born index cases and index cases of the general population

Group	No. of studies	Contacts/index case ratio (n)	Coverage (%)	TB yield (%)	LTBI yield (%)	References
Foreign-born index cases						
with close contacts	6	5.8 (5.4–12.8)	88.0 (86.3-91.1)	0.00 (0.00-0.77)	43.7 (25.5-48.9)	[12,17-19,23,24]
with non-close contacts	4	48.0 (5.5-93.4)	71.8 (70.8-83.8)	Insufficient data	15.4 (9.4-22.5)	[12,17,19,23]
General population index cases						
with close contacts	7	3.8 (3.2-5.1)	82.1 (80.3-84.2)	2.15 (2.07-2.28)	37.0 (32.9-40.2)	[15,16,20,21,24,27,29]
with non-close contacts	4	2.6 (1.8-4.1)	n.a.	0.40 (0.20-1.80)	29.0 (14.5-29.7)	[13,15,16,21]

n.a.=not applicable

- In non-EU studies, more contacts per foreign-born index case were screened, lower TST cut-off values were used to define a positive TST, and higher LTBI yields were found.

Of the nine studies with pooled results of contact investigations, three studies reported remarkably higher TB yields than the rest [16,24,27]. The study by Solsona *et al*. was conducted in the inner city district of Barcelona, where high risk groups (HIV-infected individuals, drug users, immigrants and homeless) represent a large proportion of the population [16]. In these high risk groups, higher TB rates can be expected regardless of recent infection. In the studies by Golub *et al*. and Marks *et al*., only close contacts were included and a high proportion of the contacts were foreign-born, which might explain the high TB yield found [24,27]. However, Soren *et al.* also included only close contacts, but found no active TB cases among 659 contacts investigated [20]. The study by Anderson *et al*. did not detect LTBI in any of the contacts, possibly due to underreporting and/or incomplete test results [13].

The high TB and LTBI yield found in the study by Dewan et al., a study with one foreign-born index case, might be due to transmission by another adult with TB living at the same place as the presumed index case [25]. The high number (n=475) of contacts screened per index case in the CDC study is likely related to the fact that the index case worked in the newborn nursery and maternity ward and therefore large scale contact tracing was conducted [26].

Limitations of the study

Although the focus of this study was on the effectiveness of contact tracing among the foreign-born population in EU countries, only six relevant EU studies were found from which data could be extracted. This highlights the lack of reported evidence from EU countries and indicates that more data reports are needed. The collection and reporting of data showed a high level of heterogeneity across the studies, which made the results difficult to compare and no firm conclusions could be drawn. For instance different cut-off values for a positive TST were used, i.e. ≥5mm and ≥10mm. In addition, some studies used adapted cut-off values for TST testing in BCG-vaccinated individuals [17,28] whereas others did not [25]. Not all studies mentioned if and how persons with prior positive TST results were included. Slightly different definitions were used across the studies, for instance for close and non-close contacts. In the included studies among contacts of the index cases from the general population, close contacts included more often only household contacts than in studies reporting contacts of foreign-born index cases, which more often included workplace contacts. The broader definition used by the latter studies could explain why they found a lower TB yield among contacts in this groups because of less proximity to the index case. The characteristics of the index cases differed in terms of sputum and culture status. Not all studies accounted for or reported people lost to follow-up, and the duration of contact tracing differed between studies. Some studies used a three months follow-up period, while others used a few years.

Challenges of contact tracing among foreign-born individuals

Sputum smear status of the index case

As mentioned, only six studies compared outcomes by sputum smear status. As expected, a higher LTBI yield was found among contacts of smear-positive cases compared to contacts of smear-negative patients. The yield was almost three-fold higher in foreign-born contacts.

It should be noted that this higher yield among foreign-born contacts could be due to the higher background rate of LTBI in this part of the population who acquired infection in their country of origin. It is evident that if this hypothesis holds true, contact tracing in this group of individuals should possibly be considered as a form of screening to identify latent infections not related to the index case

Standardisation of methods used to diagnose TB and LTBI in contacts

In the studies included that reported TB yield, a large variety of methods was used to detect TB. While the gold standard to detect TB disease is a positive culture of Mycobacterium tuberculosis, not all studies used this. Most studies used CXR in combination with symptom screening. In most studies, CXR was used after a positive TST was found.

For many years, LTBI has been identified using the TST. Despite its widespread use, the TST has proved to be less specific among individuals born in high-incidence countries due to cross-reaction with the BCG vaccine (see below) and with atypical mycobacteria, both of which are present in individuals from high-incidence countries [30]. In some studies, CXR was used besides the TST to assess infection. Langenskiold *et al*. and MacIntyre *et al*., for example, used both TST and CXR to define LTBI [15,28]. CXR was also used to find evidence of prior TB.

Recently, interferon gamma release assays (IGRAs) have become commercially available for the detection of LTBI. These tests have characteristics that seem to make them more suitable for screening among migrants: they do not cross-react with BCG vaccination and less frequently with atypical mycobacteria [31,32], and they seem to give a better indication of the time of infection [4]. However, there is a need to asses if the test is equally effective in people from high- versus low-incidence countries [33].

BCG vaccination status

Only four of 18 studies provided information on BCG vaccination status. This is a major drawback, as most foreign-born index cases and foreign-born contacts described in this study were from countries with a high TB incidence that have high BCG vaccination rates. Because of the possible cross-reaction induced by BCG, LTBI yield among foreign-born contacts needs to be interpreted with care for the studies that did not adjust the TST cut-off values for BCG-vaccination status, since the number of cases may have been overestimated due to false positives.

DNA fingerprinting and epidemiological linkage

The assumption underlying contact tracing is that contacts have been infected by the index case around whom the investigation is centred. However, it has been demonstrated through DNA fingerprinting that contacts can be infected by another strain of *M. tuberculosis* than the one that infected the presumed index case [21,34]. Identical DNA fingerprints between contact and index case suggest that transmission has occurred [35]. Thus, not all contacts have been infected by the presumed index case, but some have been infected by another source. Genetic characterisation of the pathogen can therefore have important implications for source finding.

In most low-incidence countries, foreign-born cases have a lower rate of clustering than local-born cases [36,37]. This is often interpreted to mean that foreign-born people develop TB as a consequence of reactivation of prior infection, the likelihood of which is related to country of origin, age at migration, socio-demographic factors, and duration of stay in the new country [5]. Moreover, a foreign-born person could have been recently infected or reinfected when visiting their country of origin, rather than by

transmission from the source case [5]. Similarly, clustering among local-born people could be due to specific sociological factors.

These findings suggest that the use of molecular typing and cluster analysis in support of traditional contact tracing should be further explored.

Stigma of TB and fear of naming contacts

Social stigma is recognised as an important barrier for successful care of people affected by TB [38]. Stigma might also prevent foreign-born index cases from naming (all of) their contacts. Fear might play a significant role in naming contacts when these are staying illegally in the country of residence. The number of exposed contacts can therefore be underreported, which can result in a bias. However, few data are available on the effect of stigma in contact tracing.

Treatment compliance

Only eight of the studies reviewed here reported the proportion of contacts who started LTBI treatment and only six studies reported treatment completion rates. These limited results did not indicate a difference in adherence between foreign-born contacts and contacts from the general population (including foreign-born). The overall adherence was 63.6%, suggesting preventive treatment can be effective. However, the benefits of treatment should be carefully balanced against the side effects such as drug-induced hepatitis [3] as well as against treating people unlikely to develop TB.

Cost-effectiveness of contact tracing

Although this was not the scope of this literature review, research indicated that contact tracing was highly cost-effective and resulted in net savings [39]. Dasgupta *et al*. reported that close-contact investigation was more cost-effective than screening of immigration applicants and surveillance programmes [39]. The latter two ways of case detection were less cost-effective largely because of substantial operational problems such as additional visits for education and reassurance, evaluation of side effects or new medical problems, or assistance with social problems, all of which are common in newly arrived immigrants.

Conclusions

From this review several conclusions can be drawn to address the challenges facing contact tracing among migrants.

Uniform contact tracing strategy

According to this study and that done by the Tuberculosis Network European Trials Group (TBNET) [40] a high variety of contact tracing strategies are being applied across and even within countries. Not every contact investigation can reasonably be conducted with the same strategy, uniform decisions about who needs to be assessed and why a certain strategy has been chosen should be agreed upon. It is therefore important to get more insight in decision making policies. Key questions to be answered are for example: which considerations are made to decide the initial size of the contact investigation? When do local health services expand the contact investigation to the next circle of contacts? Who is responsible for that decision?

Uniform data collection and reporting

To compare the effectiveness of the different contact tracing strategies used, data need to be collected and reported more uniformly. Definitions should be used uniformly throughout studies to be able to better compare results. Usage of standardised protocols might help to achieve this. International validated cut-off values are needed to define a positive TST induration, and these should be adjusted for BCG-vaccination status.

Contact tracing as a screening strategy

The findings emphasise that foreign-born people from high-incidence countries are at high risk of acquiring or having LTBI. Contact tracing could be used as a screening strategy to identify cases in a high-prevalence population and could be seen as a 'high-risk screening' exercise [7].

Targeted screening

The objective of contact tracing is to find individuals recently infected with TB who are likely to develop active disease. Those at high risk of developing active TB need to be better targeted.

There is an urgent need for a diagnostic tool to identify people with recent latent infection that are at highest risk for developing active disease. This is especially relevant among foreign-born contacts due to the challenge of interpreting the currently available tests due to, for example, BCG, HIV status, nontuberculous mycobacteria and background TB prevalence. Additional research is needed to verify whether the promising IGRAs are reliable in detecting recent infection and are suitable for use in the migrant population.

In conclusion, it should be noted that finding of higher LTBI yields in contact investigations among foreign-born contacts is not unexpected given higher background infection prevalence in these populations. Identifying for which infected contacts close follow-up or preventive treatment should be offered remains a priority. This will be key in determining the role of extensive contact tracing in the context of enhanced TB control among high-risk populations and in establishing its cost-effectiveness.

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